

Spotlight

Timing is everything: Clinical evidence supports pre-symptomatic treatment for spinal muscular atrophy

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Two new studies by Strauss et al. demonstrated safe and effective pre-symptomatic delivery of gene therapy in children with spinal muscular atrophy (SMA).^{1,2} These results highlight the importance of newborn screening programs and early therapy delivery for SMA.

Spinal muscular atrophy (SMA) arises from homozygous loss of the *Survival Motor Neuron 1* (*SMN1*) gene. This causes degeneration of lower motor neurons and muscle atrophy, as well as an array of systemic defects. In most cases, patients suffer from the severe subtype of the disease, SMA type I. Without treatment, symptoms present within six months after birth and no major motor milestone is reached. Historically, infants would not survive past the age of two. Humans have an additional copy of *SMN1*, called *SMN2*, which is alternatively spliced and only produces about ten percent of the full-length, functional SMN protein. Copy number of *SMN2* varies in SMA patients, making this gene an important modifier of disease severity.

The past decade has brought tremendous therapeutic advances for treating SMA. Three therapies are now available, each with a distinct mechanism of action and delivery strategy, and each providing a precious disease-modifying treatment.³ Nusinersen (Spinraza), an antisense oligonucleotide targeting *SMN2*, was approved by the FDA in December 2016. Onasemnogene abeparvovec (Zolgensma) was approved a couple of years later and is a gene-replacement therapy. Also targeting *SMN2*, the small molecule risdiplam (Evrysdi) is the most recently approved SMN-dependent therapy for SMA. The elevated price tag of these treatments (\$2.1 million for a single injection of Zolgensma, \$750 000 for the first year of treatment with Spinraza, and up to \$340 000 per year for Evrysdi) is in

part justified by their lifesaving and life-quality-improving capacity. While patients who respond well to treatment reach motor milestones never thought possible, benefits can vary widely. Now that such treatments are available, important questions surrounding the optimal timing and route of administration need to be addressed.

A growing number of studies indicate that SMA has a strong developmental component. Indeed, the SMN protein is crucial for—and expressed at high levels throughout—development in the nervous system, with levels decreasing after birth.⁴ A wealth of preclinical data has shown that the therapeutic time-window to treat SMA is narrow.⁵ Pathological defects have been described prenatally and point to developmental phenomena underlying motor neuron degeneration and systemic phenotypes.^{6,7} In mouse models, early treatment increases the chances of extending survival and improving motor functions. In the clinic, interim results from the phase II NURTURE trial already provided precious information confirming this effect in SMA patients.⁸ Starting nusinersen treatment pre-symptomatically in infants with two or three copies of *SMN2* provided significantly improved outcomes compared to treatment initiated in symptomatic patients.

Twin papers published in *Nature Medicine* in June 2022 describe the results of SPR1NT, a phase III clinical trial for onasemnogene abeparvovec.^{1,2} This single-dose intravenous gene-replace-

ment therapy delivers an *SMN1* transgene using a modified AAV9 vector. In SPR1NT, the treatment was tested for safety and efficacy in pre-symptomatic infants at risk of developing SMA type I or II (with two or three copies of *SMN2*, respectively). This study follows up the original trial for onasemnogene abeparvovec in 15 symptomatic SMA type I patients.⁹ Following prenatal or newborn genetic confirmation of biallelic deletion of *SMN1*, 14 infants with two copies of *SMN2* and 15 infants with three copies of *SMN2* were treated at ≤ 6 weeks of life, before symptom onset. The results from SPR1NT show that neonates treated pre-symptomatically achieved greater and earlier developmental milestones than untreated patients and patients treated once symptomatic. While the cohorts were small, the findings are unequivocal: treatment needs to be started as early as possible to maximize therapeutic benefits.

Newborn screening (NBS) is likely to be key for the delivery of such early treatment, but many countries who have the therapies available do not yet include SMA in their NBS programs. Australia, Belgium, Canada, Germany, Italy, Japan, and Taiwan have all implemented NBS programs for SMA as have 46 states in the US.^{1,10} All infants included in the SPR1NT trial were screened by NBS or prenatal testing. As well as increasing therapeutic efficacy, another benefit of pre-symptomatic treatment—and thus NBS—may be to alleviate the high financial costs arising from living with severe



SMA. For example, one study investigating Australian NBS programs revealed that the cost of NBS coupled with early gene therapy fell well within accepted thresholds for willingness-to-pay.¹⁰

The publications by Strauss et al. provide the first direct clinical evidence that pre-symptomatic treatment with gene therapy enhances its therapeutic efficacy in infants with SMA type I and II. This should encourage the SMA community and stakeholders to consider pre-symptomatic timing as optimal for therapy delivery and provide support to convince policy makers of the importance and value of NBS for SMA.

DECLARATION OF INTERESTS

T.H.G. has provided consultancy and advisory services concerning SMA therapies to Roche and Novartis. T.H.G. is chair of the clinical & scientific advisory board of SMA Europe.

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